Selecting Candidates for Radical Prostatectomy

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Men with clinically localized prostate cancer and their physicians are faced with the management decision of radical prostatectomy, radiation therapy, or watchful waiting. Who is the best candidate for radical prostatectomy? Is cure the only relevant outcomes parameter? Does age make a difference? Are imaging studies necessary? This review provides answers, step-by-step, in the decision-making process. [Rev Urol. *2000;2(3):182-189*]

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Prostate cancer is currently the second leading cause of cancer-related deaths in American males. In 1996, an estimated 300,000 cases of prostate cancer were diagnosed, and 41,000 men died of the disease.[1] Clinically localized prostate cancer is the diagnosis in an increasing proportion of men.[2] Radical prostatectomy, radiation therapy, and watchful waiting are reasonable options for the management of clinically localized prostate cancer. This article will review the issues to be considered when selecting candidates for one of these options: radical prostatectomy.

The primary indication for radical prostatectomy should be to cure prostate cancer. Therefore, the ideal candidate for radical prostatectomy is the person with disease that is pathologically confined to the prostate and who, if untreated, would suffer morbidity or mortality from the malignancy.

Because the overall morbidity and mortality associated with a prostate cancer depends not only on the aggressiveness of the tumor but also on the life expectancy of the host, selection of candidates for radical prostatectomy requires, at a minimum, a comprehensive assessment of:

- Life expectancy.
- The natural history of the diagnosed prostate cancer.
- The ability of radical prostatectomy to cure the disease.
- The morbidity of radical prostatectomy.

Influential Factors

Age and Life Expectancy. The life expectancy of men with clinically localized prostate cancer is of paramount importance in the selection of candidates for radical prostatectomy. Since clinically localized prostate cancer does not represent an immediate, life-threatening dilemma, the benefits of treatment are recognized on-

ly if the patient survives long enough to avoid future consequences of the malignancy. Many experts in the surgical management of prostate cancer advocate that radical prostatectomy should be offered only to men 70 years or younger or to those patients with life expectancies exceeding 10 years.[3-5] Although requirements for a 10-year life expectancy or an upper age limit of 70 years are both reasonable guidelines for selecting surgical candidates, the patient's general medical condition and the aggressiveness of the cancer should also be taken under consideration.

The age-dependent life expectancy of American males is presented in Table 1.[5] If one accepts a 10-year life expectancy criterion for offering radical prostatectomy, then the majority of men aged 60, more than half of men aged 70, and more than one third of men aged 75 would be appropriate candidates for surgical intervention.

Clinicians can use Table 1 as a guide during consultations regarding the management of clinically localized prostate cancer. Arbitrary adjustments can be made based on comorbidities. The life expectancy data should be superimposed on the natural history data to determine ultimately the probability that treatment will have a favorable impact on the course of the disease process.

Natural History. The natural history of a disease refers to the progression of the untreated disease over time. Since not all men with a diagnosis of prostate cancer are at risk from their malignancy, assessing the natural history of a prostate cancer is a very important factor in selecting candidates for radical prostatectomy.

It is of paramount importance to discuss at great length with patients the natural history of prostate cancer, since the public is being bombarded with information (or misinformation) about the overtreatment of prostate cancer. Summarizing the following 3 studies will address the controversies related to the natural history of prostate cancer.

Table 1
Life Expectancies of American Males

	Probability of survival (%)			
Baseline age (year)	5-year	10-year	15-year	20-year
50	96	90	82	71
55	94	85	74	60
60	91	79	64	46
65	87	70	50	29
70	81	58	34	15
75	72	42	18	5

The first study, by Johansson and associates,[6] claimed that only 8.5% of 223 men presenting with clinically localized prostate cancer and managed with deferred treatment died of the disease. This observation has been widely misinterpreted to support watchful waiting for all men with newly diagnosed clinically localized prostate cancer. In this retrospective study, the average age of men at the time of diagnosis was 72 years, and the follow-up period, in some cases, was less than 7 years. Forty-seven percent died of competing illnesses, and 67% of the tumors were well differentiated. Thus, the profile patient is not representative of the typical patient who is considering prostatectomy[4,7,8] (Table 2). The "typical" patient reported by Johansson and colleagues was elderly, was unhealthy, and had a low-grade malignancy, and their conclusions cannot be generalized to apply to the majority of men with a diagnosis of clinically localized prostate cancer.

It is also important to point out that death is not the only consequence of untreated prostate cancer. Of the subjects reported by Johansson and colleagues, 53% developed progressive disease, and 29% underwent hormonal therapy and experienced hot flushes, decreased libido, and impotence. My interpretation of this study is that even a proportion of patients deemed inappropriate candidates for radical prostatectomy because of age, comorbidities, and minimally aggressive disease will suffer clinically significant consequences of prostate cancer.

The second study, a retrospective report by Albertsen and coworkers,[9] compared the survival of men aged 65 to 75 who had clinically localized prostate cancer (diagnosed between 1971 and 1976) and were treated with hormonal therapy with age-matched controls. Of the 334 evaluable patients with known Gleason scores, the percentages with well, moderately, and poorly differentiated prostate cancers were 13%, 48%, and 39%, respectively. The tumor characteristics were comparable to those of men undergoing radical prostatectomy for clinically localized disease (Table 2). The important finding of this study is that the mean survival of men with a diagnosis of moderately and poorly differentiated clinically localized prostate cancer was significantly decreased, compared with controls (Table 3). Only in the small subset of men with well-differentiated tumors was there no observed, statistically significant difference in survival relative to age-matched controls. Thus, watchful waiting should be considered a legitimate option for men older than 65 with well-differentiated tumors.

The third study is a recent retrospective analysis reported by Aus and coworkers[10] of 301 Scandinavian men with clinically localized prostate cancer managed with deferred treatment.

Table 2
Age and Tumor Grade of Men Treated With Radical Prostatectomy vs Deferred Treatment

	N	Age (year)	Gleason score (%) 2–4	5–7	8–10
Deferred treatment					
Johansson (1992)[6]	223	72	66	30	4
Albertsen (1995)[9]	334	NR*	13	48	49
Aus (1995)[10]	297	NR*	33	39	28
Radical prostatectomy					
Partin (1993)[8]	955	59.4	11	86	4
Zincke (1994)[4]	3170	65.3	9	66	25
Catalona, Smith (1994)[7]	925	63.9	21	66	13

*NR, not recorded.

The study population included all men in a Swedish community who died between 1988 and 1990. The cause of death, the presence or absence of prostate cancer, and the age at the time of diagnosis of prostate cancer were evaluable for the entire study cohort. The probability of dying of (not with) prostate cancer, based on age at time of diagnosis, is presented in Table 4. The probability that a 70-year-old Scandinavian man with a diagnosis of localized prostate cancer died of prostate cancer was approximately 50%. Based on this information, arbitrarily assuming that prostate cancer is not a clinically significant disease for men 70 years of age is a gross misrepresentation of the data related to the natural history of this disease.

The fact that a detected cancer has the potential to be aggressive and life-threatening does not indicate that intervention will achieve a cure. The curability of prostate cancer at the time of diagnosis is, therefore, a third factor that should be considered in selecting candidates for radical prostatectomy.

Predicting Curability. The cure of prostate cancer requires complete extirpation or destruction of all prostate cancer cells, since there is no compelling evidence that hormonal therapy or chemotherapy increases survival in men with localized or advanced disease. The probability of achieving a cure following radical prostatectomy strongly influences the risk-benefit ratio of intervention. Since localized prostate cancer often has a protracted natural history, long-term follow-up data are mandatory to legitimize claims related to cure.

The radical prostatectomy series of Walsh and colleagues[8,11-13] has become the benchmark for the surgical management of prostate cancer in the modern era. Of the 955 radical prostatectomies performed by Walsh between April 1982 and March 1991, only 2% were stage T1c. Of the radical prostatectomies performed by me between January 1994 and December 31, 1997, more than 80% presented with clinical stage T1c. Therefore, the majority of cases in the Walsh series with 15-year follow-up were not detected by prostate-specific antigen (PSA) screening. Since T1c tumors are more likely to be organ-confined than are T2 tumors, Walsh's 15-year disease and biochemical disease-free survival data will likely improve with additional follow-up. The overall 5- and 10-year cause-specific survival rates in the Walsh series were 96% and 93%, respectively.[8]

The follow-up of most contemporary surgical series is currently too short to make definitive claims regarding survival and surgical cure. In the absence of these survival data, pathologic stage and postoperative serum PSA measurements have become secondary end points for assessing surgical cure. Overall, 87% and 71% of men in the Walsh series had no evidence of biochemical recurrence 5 and 10 years following radical prostatectomy.[8] Pathologic stage and Gleason score were the best predictors of biochemical failure.

As the large contemporary radical prostatectomy series of Walsh and others achieve more reliable 15-year (and longer) follow-up, clinical, pathologic, and biochemical factors that predict the curability of prostate cancer will be defined with very narrow confidence intervals. Until these long-term follow-up data are available, we must continue to rely on clinical and biochemical surrogate end points to predict pathologic stage. Several investigators have examined the correlations between the preoperative serum PSA value, Gleason score, and clinical stage and the pathologic stage.[14,15] All of these preoperative clinical factors are independently pre-

Table 3
Effect of Clinically Localized Prostate Cancer on Survival

Baseline age (year)	No cancer	Mean survival (years) Gleason grade 2–4	Gleason grade 5–7	Gleason grade 8–10
65	15.8	16.1	11.3	7.9
70	12.7	13	8.8	5.9
75	10	10.2	6.7	4.4

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dictive of pathologic stage. Multivariate analysis demonstrates that the predictive value of pathologic stage is increased when all 3 factors are considered simultaneously. The composite nomogram of Partin and colleagues[16] is an excellent reference when selecting a candidate for radical prostatectomy. Although these nomograms predict pathologic stage, there is no consensus as to when surgical intervention is no longer advisable. Many younger men with the probability of an organ-confined tumor that comprises only 25% of the prostate may select radical prostatectomy, since the prospect of dying of their disease is virtually 100% if their cancer is left untreated.

The goal of preoperative staging is to exclude those patients who are unlikely to be rendered disease-free following radical prostatectomy. It is generally assumed that the presence of gross capsular penetration, seminal vesicle invasion, lymph node metastases, and systemic metastases diminishes the probability of a surgical cure to the point that the wisdom of radical prostatectomy must be seriously questioned. There are no data to support or refute whether a noncurative radical prostatectomy increases survival or improves quality of life by achieving local disease control or reducing the risk of metastasis. In the absence of a randomized study comparing radical prostatectomy with deferred treatment in high-risk candidates for extraprostatic disease, my opinion is that radical prostatectomy is of little or no value in this clinical setting.

Imaging diagnostic studies are routinely obtained to exclude men who are unlikely to benefit from radical prostatectomy. Gross seminal vesicle invasion and extracapsular penetration (clinical stage T3 disease) are likely to be detected at the time of digital rectal examination or by CT, transrectal ultrasonography, or MRI. If surgical candidates have extraprostatic disease, it is most typically at the microscopic level. The limitation of clinical staging is its lack of sensitivity and specificity for detecting microscopic capsular penetration or seminal vesicle invasion.[17]

CT is routinely used preoperatively to detect pelvic lymph node metastasis. Epstein and coworkers[18] reported that approximately 10% of patients with clinically localized carcinoma of the prostate will have metastasis to the pelvic lymph nodes. This incidence is higher than in more contemporary surgical series. Nevertheless, only 1% of the positive-staging pelvic lymphadenectomies were found to have sufficient volume of nodal disease to be detected by CT. Therefore, CT is not a reasonable staging modality for identifying pelvic lymph node metastases in patients with clinically localized carcinoma of the prostate. There is no reason to suspect that a pelvic MRI would be more likely to detect micrometastatic lymph node metastasis.

Table 4
Probability of Dying of Cancer for Men With Clinically Localized Prostate Cancer Treated With Noncurative Intent

Age at diagnosis (year)	Probability of dying of cancer (%)
50-55	100
56-60	75
61-65	75
66-70	60
71-75	50
76-80	40

The Prostascint scan uses indium 111–labeled CYT-356 (an antibody conjugate directed to a glycoprotein found primarily on the cell surface membranes of prostate tissue) to identify residual prostate cancer in the prostate bed or metastasis to lymphatic tissue, soft tissue, or bone.[19] The sensitivity and specificity of this scan for detecting pelvic lymph nodal metastasis in a large consecutive cohort of surgical candidates undergoing lymphadenectomy has not been reported.

The skeletal system represents the predominant site of systemic prostate cancer metastases. The primary limitation of a radionuclide bone scan for identifying skeletal metastasis is its lack of specificity. Chybowski and colleagues[20] reported that radionuclide bone scans were always negative in subjects with serum PSA levels lower than 15 ng/mL. With this in mind, I do not routinely obtain a bone scan on patients with PSA levels lower than 15 ng/mL, provided the tumor is not poorly differentiated and there are no new musculoskeletal symptoms.

The majority of urologists obtain routine CT, MRI, and radionuclide bone scans on all candidates for radical prostatectomy. The evidence suggests that the routine use of these studies provides little or no clinically relevant information that will influence management. In an era of cost containment, there are many opportunities to reduce costs without compromising quality of care. The annual cost savings achieved by simply eliminating these unnecessary diagnostic tests will exceed $450 million.

The limitations of imaging for the staging of prostate cancer have provided the opportunity to develop novel strategies for determining which surgical candidates are at high risk for treatment failure. Katz and coworkers[21] reported that the reverse transcriptase-polymerase chain reaction (RT-PCR) assay for PSA was a useful predictor of extraprostatic disease in

men undergoing radical prostatectomy. Of those men assayed with documented systemic skeletal metastasis, only 75% were found to have a positive RT-PCR assay for PSA. It is difficult to imagine that this assay reliably discriminates between organ-confined and microscopic extraprostatic disease when the assay is undetectable in 25% of patients with diffuse skeletal metastasis.

Lymphadenectomy is often routinely performed at the time of radical prostatectomy. Most urologists will abort the radical prostatectomy if the frozen-section diagnosis shows lymph node involvement, since there is no evidence that removing the prostate results in a survival advantage.

The probability of positive lymph nodes can be predicted from the preoperative serum PSA level, clinical stage, and Gleason score.[16] If the probability of lymph node metastasis is lower than 2%, I no longer perform a staging pelvic lymphadenectomy, since I believe the risk of 98 "unnecessary pelvic lymphadenectomies" exceeds that of 2 such procedures. I do not perform a staging pelvic lymphadenectomy if both the Gleason score is lower than 6 and the serum PSA value is lower than 10 ng/mL.

In summary, serum PSA level, clinical stage, and Gleason score should be used routinely to predict the pathologic stage of radical prostatectomy candidates, recognizing the inherent limitation of pathologic stage in predicting cure. Imaging studies, the RT-PCR assay for PSA, and scintigraphy are expensive and have no proven role in the selection of candidates for radical prostatectomy.

Morbidity of Radical Prostatectomy. The decision to select radical prostatectomy should also be influenced by the morbidity of the surgical intervention. Surgical candidates must ultimately balance the risks and benefits of treatment. The intraoperative and perioperative risks of surgery can be accurately ascertained from the literature; the benefits of surgery are more difficult to define.

Main Points

- A 10-year life expectancy or an age limit of 70 years is a reasonable guideline for selecting surgical candidates, but the patient's medical condition and the aggressiveness of the cancer must be taken into account as well.
- Men older than 65 years with small, well-differentiated tumors may be candidates for watchful waiting.
- The predictive value of the pathologic state is increased preoperatively when serum prostate-specific antigen (PSA) value, Gleason score, and clinical stage are considered simultaneously.
- Routine use of CT, MRI, and radionuclide bone scans for all candidates for radical prostatectomy provides little or no information to aid in management decisions.
- A staging pelvic lymphadenectomy may not be necessary if the Gleason score is lower than 6 and the serum PSA value is lower than 10 ng/mL.
- Lack of reliable, objective outcomes data makes it impossible to compare directly the morbidity of radical prostatectomy with that of radiation therapy.
- The priorities of the patient are key to management decisions for clinically localized prostate cancer.

The overall morbidity of radical prostatectomy includes intraoperative and perioperative complications and the impact of impotence and incontinence on quality of life. Since 1994, I have performed more than 1000 radical retropubic prostatectomies without a single operative mortality. One man died of myocardial infarction (MI) at home within 30 days of surgery. Only 1 case required reoperation within the first 30 days of the original procedure. The rate of technical complications in this series, including rectal injuries, is 0.4%, and of ureteral injury, 0.1%. There was a single case of a prolonged ileus (0.1%). The incidence of cardiovascular complications includes MI (0.15%), cardiovascular accident (0%), pulmonary embolism (0.3%), and deep venous thrombosis without pulmonary embolism (0.4%). These mortality and morbidity rates compare favorably with other large radical prostatectomy series.[22] Based on my experience, surgical candidates are counseled that the risk of a life-threatening intraoperative or perioperative complication is approximately 1%. Radical prostatectomy can be offered with the expectation of an uneventful hospitalization and recovery. Of the 251 radical prostatectomies I performed in 1999, the mean length of hospital stay was less than 2 days. Hospital discharge was permitted only if the pelvic drain was removed and the patient was afebrile and tolerating a regular diet.

The primary long-term complications associated with radical prostatectomy are incontinence and erectile dysfunction. The incontinence rates reported in the literature vary between 5% and 31%.[23-29] This wide range of incontinence rates most likely reflects different definitions of continence, different mechanisms for assessing continence, and the varying technical abilities of the surgeons. I counsel patients that total incontinence is rarely (if ever) associated with radical prostatectomy. I emphasize that it may take up to 1 year to regain maximal urinary continence and that 10% to 15% of men will have some degree of permanent stress incontinence. Of the men with any degree of stress incontinence, approximately half wear 1 small protective shield over a 24-hour interval, so the incontinence is of little or no bother. The remaining patients require 1 to 3 shields (not diapers) a day; this degree of incontinence does have some impact on quality of life. Interestingly, 96% of patients undergoing radical prostatec-

tomy are satisfied or very satisfied with their treatment decision and overall outcome.

Approximately one third of men older than 50 years have moderate or severe urinary tract symptoms.[30,31] In our series, radical prostatectomy significantly improved the American Urological Association (AUA) symptom score in men presenting with moderate or severe symptoms. In men with a baseline AUA symptom score of 8 or greater, the mean AUA symptom score decreased from 12.8 to 6.1 at 1 year following radical prostatectomy. This 52% decrease in the AUA symptom score is comparable to outcomes following transurethral prostatectomy.[32] The favorable effect of radical prostatectomy on lower urinary tract symptoms counterbalances the negative effects caused by incontinence.

Preservation of potency following nerve-sparing radical prostatectomy ranges from 20% to 70%.[7,24,27,33,34] The preservation of potency depends on age, clinical stage, and the preservation of one or both neurovascular bundles. It is important to emphasize that the majority of men who are rendered impotent maintain a normal libido and that the pleasure derived from orgasm may not be significantly altered. Thus, couples can achieve sexual intimacy without an erection. For couples for whom intercourse is essential for intimacy, erections can be restored pharmacologically by intracavernous, intraurethral, or oral treatment.

The morbidity of radical prostatectomy is limited primarily to incontinence, impotence, and an occasional non–life-threatening technical or medical complication. The morbidity of advanced prostate cancer includes urinary retention, lower urinary tract symptoms, gross hematuria and clot retention, ureteral obstruction, painful bony metastases, and spinal cord compression. The morbidity of palliative intervention for advanced disease, such as transurethral prostatectomy and hormonal therapy, includes incontinence, impotence, and hot flushes. The morbidity of advanced prostate cancer and its treatment exceeds the risk of radical prostatectomy by an overwhelming margin. The obvious challenge is to determine which individuals with surgically curable disease are at risk for developing advanced disease and to offer these patients radical prostatectomy.

Radical Prostatectomy vs Radiation Therapy

In the absence of a large-scale, randomized study with 15-year follow-up comparing both the effectiveness and morbidity of radical prostatectomy with radiation therapy, claims regarding optimal treatment of localized prostate cancer cannot be definitively supported. The only randomized study comparing radical prostatectomy with radiation therapy, with a mean follow-up of 8 years, showed a survival advantage for radical prostatectomy.[35] The survival advantage of radical prostatectomy became apparent with longer follow-up. Despite the lack of randomized, long-term comparative studies, physicians must interpret the existing literature and provide treatment recommendations for those patients with localized prostate cancer.

Both radiation therapy and surgery have undergone important modifications that have diminished treatment-related morbidity. The impact of these modifications on survival requires longer follow-up.

Because of the lack of reliable and objective outcomes data, it is not feasible to compare directly the morbidity of radical prostatectomy with that of radiation therapy. Serious, life-threatening complications are exceedingly rare following both radical prostatectomy and radiation therapy. The complications most commonly associated with both treatments have quality-of-life implications. Conformal external beam and interstitial radiation cause erectile dysfunction, lower urinary tract symptoms, rectal bleeding, both rectal and urinary urgency and, very occasionally, urinary incontinence. The quality-of-life complications of radiation therapy often become clinically evident over time, whereas they improve following radical prostatectomy. The majority of my patients who have undergone radical prostatectomy and adjuvant external beam radiotherapy have indicated that overall recovery from surgery was easier.

Since the intraoperative risks increase and the survival advantage decreases following radical prostatectomy as a function of age, there does appear to exist a cohort of men with localized prostate cancer for whom radiation therapy may represent the preferred management. The specific profile of this group has yet to be defined.

Summary

Selecting candidates for radical prostatectomy is a challenging process for both physician and patient. The life expectancy of the patient, the natural history and curability of the prostate cancer, and the morbidity of treatment and deferred treatment must be critically examined. Although the available clinical data providing this information have inherent deficiencies, all of these variables can be estimated with reasonable accuracy. A concerted effort should be made to provide the patient with prognostic information that is relevant to his age, his health status, and the stage and grade of the cancer. The patient must be intimately involved in the decision making, since not all men selecting radical prostatectomy will ultimately need or benefit from surgical intervention.

A randomized study comparing radical prostatectomy, radiation therapy, and watchful waiting that has objective quality-of-life measurements and follow-up to the time of death would undoubtedly provide the objective and conclusive data required to

make definitive treatment decisions. Nevertheless, educated decisions related to the management of clinically localized prostate cancer must and can be derived from the present literature. The available data provide compelling evidence that prostate cancer has a clinically significant impact on survival and that radical prostatectomy cures prostate cancer. Although a randomized study may more precisely establish the age threshold for treatment, many younger men participating in the study would be denied a cure and would die prematurely of their prostate cancer. Because of the inherent uncertainties of life expectancy and the biologic activity of the cancer, a randomized study will never provide definitive recommendations for the individual patient. Thus, the patient and his priorities will always play a pivotal role in decisions related to the management of clinically localized prostate cancer. ■

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